UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/840,872	04/25/2001	Antonio J. Grillo-Lopez	P 0280609/2000-30-154A	4921

909 7590 04/10/2006

PILLSBURY WINTHROP SHAW PITTMAN, LLP
P.O. BOX 10500
MCLEAN, VA 22102

EXAMINER	
NICKOL, GARY B	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 04/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/840,872	GRILLO-LOPEZ, ANTONIO J.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56-60 and 62-74* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56-60 and 62-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Re: Grillo-Lopez, A.

Response to Arguments

The response filed January 12, 2006 in response to the Office Action of July, 12, 2005 is acknowledged and has been entered.

Claims 56-60 and 62-74 remain under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections Maintained:

Claims 56-60, and 62-74 remain rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,776,456 (Anderson *et al.*) in view of U.S. Patent No. 6,042,826 (Caligiuri *et al.*) and DeAngelis, LM (J.Neurooncol. Vol. 38 (2-3), 1998, pages 245-252) for the reasons of record.

Applicants argue (Response, page 3) that after a review of the cited references, one skilled in the art would not reasonably believe that the presently claimed methods could be practiced with an expectation of achieving therapeutic efficacy. Applicants argue (Response page 4) that no reasonable chance of success would be expected due to the "inherent unpredictability in treatment for CNS lymphomas". Applicants argue that the Anderson reference does not

provide specific guidance with respect to CNS malignancies and that Caligiuri *et al.* and DeAngelis, L. do not provide any "suggestion whatsoever that the presently claimed anti-CD20 therapies could be reasonably employed in the treatment of CNS malignancies, and therefore, cannot cure the inherent deficiency of Anderson."

These arguments have been carefully considered but are not found persuasive because they reiterate the same arguments previously presented (See Applicant's responses filed: 05-12-2004, 09-27-2004, 10-20-2004, and most recently, 04-13-2005).

Applicants further submit a declaration under 37 C.F.R. 1.132 by the affiant, Dr. Ellen Garber. Applicants argue that her viewpoint regarding the expectation of success in performing the claimed invention is relevant to a determination of non-obviousness of the invention.

Dr. Garber initially appears to argue against the teachings of the DeAngelis reference. For example, Dr. Garber argues (Item 12, page 2) that she disagrees with the examiner's suggestion that the "ongoing use of chemotherapy drugs by intrathecal administration, as summarized by DeAngelis, has predictive value regarding the therapeutic efficacy or safety of other drugs." Dr. Garber further contrasts the chemotherapeutic drugs discussed by DeAngelis versus the mechanism of action and therapeutic efficacy of targeting antibodies (Items 13-16) wherein she argues that notwithstanding the structural differences and distinct modes of action of chemotherapeutic drugs compared to therapeutic antibodies, "direct brain administration of any therapeutic agent remains highly unpredictable due to the unique brain environment and the risk of neurotoxicity".

This argument has been carefully considered but is not found relevant. Applicants are reminded that the DeAngelis reference was used as a secondary teaching that directly taught the

inclusion of certain known chemotherapeutics (i.e., methotrexate and ^{111}In-diethylenetriamine pentaacetic acid) when treating neoplasms of the brain (See action mailed 12-12-2003, top of page 5), *not* whether there was any predictive value associated with the therapeutic efficacy of treating such brain disorders. On the contrary, the predictive value (or reasonable expectation of success) associated with the treatment of CNS lymphomas with therapeutic antibodies was specifically taught by U.S. Patent No. 6,042,826 (Caligiuri *et al.*).

Dr. Garber further seeks to dismiss the obviousness rejection based on the differences between the antibodies administered in the Anderson patent (anti-CD 20 antibodies) and those administered to treat CNS lymphomas in the Caligiuri patent (anti-Fas antibodies). Dr. Garber argues (Item 21) that following a review of the Caliguiri patent, she would not conclude that anti-CD20 antibodies could be reasonably predicted to have therapeutic benefit when administered intrathecally because "anti-Fas antibodies and anti-CD20 antibodies recognize distinct antigens and confer therapeutic effects by entirely different modes of action". Dr. Garber argues that the mechanism of anti-CD20 antibodies includes ADCC, CDC (Item 22) and apoptosis (Item 33) whereas anti-Fas antibodies are limited to cell killing by apoptosis (Item 34). Thus, when viewed within the confines of the CNS, Dr. Garber argues (Item 31) that despite the presence of NK and macrophage activity in the CNS, the CNS immune inhibitory and anti-inflammatory mechanisms physiologically "outbalance and counteract immune activity". Indeed, applicants argue (Response, page 7), that the dependence on immune system effector cells, whose activity is limited in the CNS, is one reason why the therapeutic efficacy of anti-CD20 antibodies in the treatment of CNS lymphomas was unexpected. To validate this point, Dr. Garber points to the teachings of Friese *et al.* (2004). However, the Friese reference was

published four years *after* the filing date of the present application, and it's not clear if the assumption of non-enablement would have been relevant at the time of filing, especially in view of the teaching of administering targeted antibodies to B-cell lymphomas in the CNS according to the teachings of Caligiuri *et al.* Moreover, it would appear that the mechanism of cell killing by ADCC via the claimed anti-CD20 antibodies was not fully appreciated until after the filing date of the instant application because the reference relied upon (Treon, 2005, IDS) was post-filing date evidence. Generally, the state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date. Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1325-26 (Fed. Cir. 2004). Further, publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. Thus, it is not clear why the therapeutic result was surprising to applicants because applicants did not appear to have fully understood the mechanism of action of anti-CD20 antibodies *at the time* the invention was filed. Also, the Friese *et al.* reference clearly teaches that natural killer cells are present in the CNS, and Dr. Garber notes (Item 23) that natural killer cells facilitate ADCC mechanisms. Further, both anti-Fas and anti-CD20 antibodies can induce direct cell death via apoptosis (Dr. Garber, Item 33). Thus, applicant's arguments have not been found persuasive, and the rejection is maintained.

Claims 56-60, and 62-74 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,776,456 (Anderson *et al.*) in view of the teachings of U.S. Patent No. 6,042,826 (Caligiuri *et*

al.) and DeAngelis, LM (J.Neurooncol. Vol. 38 (2-3), 1998, pages 245-252) for the reasons of record and for the reasons set forth above. Applicants reiterate their arguments as set forth above. Thus, applicant's arguments have not been found persuasive and the rejection is maintained.

No claim is allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 571-272-0835. The examiner can normally be reached on M-Th, 8:30-5:30; alternate Fri., 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gary B. Nickol Ph.D.
Primary Examiner
Art Unit 1642

GBN

GARY B. NICKOL, PH.D.
PRIMARY EXAMINER